Lipid Apheresis

Policy Number:  8.02.04   Last Review: 7/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for low-density lipid apheresis when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
LDL apheresis may be considered medically necessary in patients with homozygous familial hypercholesterolemia as an alternative to plasmapheresis.

LDL apheresis may be considered medically necessary in patients with heterozygous familial hypercholesterolemia who have failed diet therapy and maximum tolerated combination drug therapy AND meet the following FDA-approved indications: (All LDL levels represent the best achievable LDL level after a program of diet and drug therapy.)

1. Functional hypercholesterolemic heterozygotes with LDL ≥ 300 mg/dL, or
2. Functional hypercholesterolemic heterozygotes with LDL ≥ 200 mg/dL AND documented coronary artery disease

When Policy Topic is not covered
LDL apheresis is considered investigational for other uses, including nonfamilial hypercholesterolemia, sudden sensorineural hearing loss, severe diabetic foot ulcerations, peripheral artery disease, preeclampsia, and non-arteritic acute anterior ischemic optic neuropathy.

Therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion is considered investigational.

Considerations
Familial hypercholesterolemia (FH) has indicated low-density lipoprotein cholesterol (LDL) less than coronary artery disease.

Documented coronary artery disease includes a history of myocardial infarction, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, and other ischemic events.
or alternative revascularization procedure, or progressive angina documented by exercise or non-exercise stress test.

Because LDL apheresis represents a chronic, lifelong therapy, Plans may consider requiring precertification or prior approval to ensure that the patient meets the patient selection criteria.

Frequency of LDL apheresis varies, but typically averages about once every 2 weeks to obtain an interapheresis level of LDL cholesterol at less than 120 mg/dL. Patients with homozygous FH may be treated more frequently. Patients are simultaneously treated with diet and drug therapy.

There is a CPT a code 36516; Therapeutic apheresis; with extracorporeal selective adsorption or selective filtration and plasma reinfusion. Although code 36516 is not specific to LDL apheresis, this code does generally encompass LDL apheresis. There is no specific CPT or HCPCS code for the disposable supplies associated with LDL apheresis. For example, dextran sulfate systems (e.g., Liposorber LA-15 System) require the use of a disposable column consisting of dextran sulfate ligands on cellulose beads.

There is a HCPCS code specific to the HELP procedure: S2120; Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation.

There is a category III CPT code for selective HDL delipidation and plasma reinfusion:

0342T: Therapeutic apheresis with selective HDL delipidation and plasma reinfusion.

**Description of Procedure or Service**

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<td>Comparators of interest are: • Medical management with lipid-lowering medications • Plasmapheresis</td>
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<td>Low-density lipoprotein apheresis</td>
<td>Standard of care</td>
<td>Symptoms, Change in disease status, Treatment-related morbidity</td>
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</table>
### Individuals:
- With acute coronary syndrome

### Interventions of interest are:
- Selective high-density lipoprotein delipidation and plasma reinfusion

### Comparators of interest are:
- Medical management with lipid-lowering medications

### Relevant outcomes include:
- Overall survival
- Disease-specific survival
- Change in disease status
- Morbid events
- Treatment-related morbidity

This use of lipid apheresis has been proposed as a treatment for various types of familial hypercholesterolemia (FH), other significant hyperlipidemia and to reduce atherosclerosis in cardiovascular disease. Lipid apheresis discriminately remove low-density lipoprotein (LDL) particles from the plasma while leaving other factors intact, allowing the filtrated plasma to be returned to the patient.

For individuals with homozygous FH who receive lipid apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies and 1 systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have shown that drastic lowering of LDL by lipoprotein apheresis increases longevity in homozygous FH. Studies have reported reductions in low-density lipoprotein cholesterol (LDL-C) levels after apheresis ranging from a mean of 57% to 75%. Currently the direct evidence is insufficient to demonstrate that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. Any future RCTs to comparing apheresis alone with no intervention or usual care or apheresis plus drug therapy with drug therapy alone will not be feasible and unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a last resort when maximally tolerated pharmacotherapy fails to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with heterozygous FH who receive lipid apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies as well as a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have shown that drastic lowering of LDL using lipoprotein apheresis decreases cardiovascular morbidity in FH heterozygotes refractory to or intolerant of statins. Studies have reported reductions LDL-C levels after apheresis ranging from a mean of 58% to 63%. Currently the direct evidence is insufficient to demonstrate that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. Any future RCTs to comparing apheresis alone with no intervention or usual care or apheresis plus drug therapy with drug therapy alone will not be feasible and unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a last resort when maximally tolerated pharmacotherapy fails to achieve target LDL-C levels. The
evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with non-FH who receive lipid apheresis, the evidence includes multiple nonrandomized (prospective and retrospective) cohort studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have reported improvements in lipid levels pre- and posttreatment. Randomized trials in patient populations, well-characterized in terms of previous treatments, lipid levels, and comorbidities, are needed to demonstrate improvements in health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with treatment-resistant nephrotic syndrome who receive lipid apheresis, the evidence includes multiple nonrandomized prospective and retrospective cohort studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. These studies, which used variable schedules of LDL apheresis with short-term follow-up, have reported that LDL apheresis may improve proteinuria and lipid abnormalities in patients with steroid-resistant nephrotic syndrome. Additional studies with concurrent controls and longer term follow-up are needed to determine that outcomes are improved with use of LDL apheresis in nephrotic syndrome. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with sudden sensorineural hearing loss who receive lipid and fibrinogen apheresis, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. One RCT compared LDL apheresis with standard treatment of prednisolone, hydroxyethyl starch, and pentoxyphylline; it reported no statistically significant differences in hearing recovery between the 2 groups. The second RCT compared combination of a single lipid apheresis procedure plus standard treatment with standard treatment alone; it reported statistically significant differences in hearing recovery with the addition of apheresis to standard treatment. An a priori primary end point, power calculations, and statistical plan to control for type I error for multiple comparisons was not reported in the second trial. Further evaluation and replications of these findings are required given the conflicting reports. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with severe diabetic foot ulcerations who receive lipid apheresis, the evidence includes a single prospective case series. Relevant outcomes are symptoms, change in disease status, morbid events, and treatment-related morbidity. In the case series, patients underwent between 1 and 7 treatment procedures and were followed for 2 to 73 months. Authors reported improved wound healing and reductions in the risk of lower leg amputations, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals with peripheral artery disease who receive lipid apheresis, the evidence includes a single prospective case series. Relevant outcomes are change in disease status and treatment-related morbidity. Improvements in symptomatic parameters such as coldness, numbness, and resting pain were reported, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with peripheral artery disease who receive lipid apheresis, the evidence includes a prospective case series. Relevant outcomes are overall survival, disease-specific survival, change in change in disease status, morbid events, and treatment-related morbidity. Improvement in gestation was reported, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with non-arteritic acute anterior ischemic optic neuropathy who receive lipid apheresis, the evidence includes a prospective case series. Relevant outcomes are symptoms, change in change in disease status, and treatment-related morbidity. Improvement in visual outcomes was reported, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with acute coronary syndrome who receive selective high-density lipoprotein (HDL) delipidation and plasma reinfusion, the evidence includes an RCT. Relevant outcomes are overall mortality, disease-specific survival, change in change in disease status, morbid events, and treatment-related morbidity. Results have shown improvements in certain biochemical measures (eg, pre-beta-like HDL and alpha HDL levels). There was no significant change in atheroma volume. Larger randomized trials with longer follow-up and clinically relevant outcomes are needed to determine the impact of delipidated HDL plasma for acute coronary syndrome. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

**Lipid Apheresis**

Lipid apheresis (also referred to as low-density lipoprotein [LDL] apheresis) involves the extracorporeal removal of apo B–containing lipoproteins, including LDL, lipoprotein(a), and very low-density lipoprotein.

The patient initially undergoes an apheresis procedure to isolate the plasma. The LDLs are then selectively removed from the plasma by either immunoabsorption, heparin-induced extracorporeal LDL precipitation (referred to as HELP), dextran sulfate adsorption, or double-filtration plasma pheresis of lipoprotein. In immunoabsorption, polyclonal antihuman apo B antibodies from sheep selectively bind and remove LDL. (Apo B is the protein moiety of LDL.) In HELP, LDL and other particles containing apo B are precipitated by heparin at an acidic pH. Dextran sulfate adsorption removes LDL by binding the positively charged apo B to dextran sulfate particles bound to cellulose.
Therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion is a procedure in which plasma is removed from the body by apheresis, processed through a delipidation device and then returned to the patient. The delipidation procedure selectively removes cholesterol from HDL, converting the major alpha HDL to pre-beta-like HDL. The plasma with pre-beta-like HDL is then reinfused to the patient. The pre-beta-like HDL is a form of HDL that enhances cholesterol transport to the liver and is thought to reduce atherosclerosis development and burden.

Diseases Treated with Lipid Apheresis
Lipid apheresis is used for disorders with marked hyperlipidemia, primarily familial hypercholesterolemia (FH). FH is a dominantly inherited disorder involving a mutation of the gene that encodes for the specific cell surface receptor responsible for LDL uptake by the cells. The heterozygous form affects about 1 in 500 people. The number of LDL receptors is halved in this condition, resulting in serum low-density lipoprotein cholesterol (LDL-C) levels that are approximately 2 to 3 times levels that are considered acceptable (ie, >300 mg/dL). Affected male patients typically develop coronary heart disease in their thirties and forties, while women develop coronary heart disease in their fifties. Depending on the patient, heterozygous FH may or may not respond adequately to lipid-lowering drugs.

Homozygous hypercholesterolemia is rare, occurring only in 1 in 1 million subjects. Serum levels of LDL-C may be elevated 6-fold (>500 mg/dL), due to the total lack of functioning LDL receptors. Homozygotes may develop severe aortic stenosis and coronary heart disease by age 20 years. These patients typically do not adequately respond to drug or diet modification therapy. In the past, patients with homozygous FH may have been treated with plasma exchange, but the advent of LDL apheresis provides a more targeted approach by permitting selective removal of LDL from the plasma.

Regulatory Status
Two lipid apheresis systems have received approval from the U.S. Food and Drug Administration (FDA) for marketing. In February 1996, dextran sulfate device “Liposorber LA-15® System” (Kaneka Pharma, New York City, NY) was approved by the FDA through the premarket approval process for use to “acutely remove LDL-C from the plasma of high risk patient populations for whom diet has been ineffective or not tolerated.”

In October 2013, the Liposorber LA-15 System received approval for additional indications through the humanitarian device exemption process for the treatment of pediatric patients with primary focal segmental glomerulosclerosis, when the following conditions apply:

- Standard treatment options, including corticosteroid and/or calcineurin inhibitor treatments, are unsuccessful or not well-tolerated, and the patient has a GFR [glomerular filtration rate] ≥60 mL/min/1.73 m² OR
- The patient is post-renal transplantation.
In September 2007, heparin-induced extracorporeal LDL precipitation “HELP® System” (B. Braun, Melsungen, Germany) was approved by the FDA through the premarket approval process for use in the above indication.

There are no devices FDA approved specifically for HDL delipidation. The Lipid Sciences Plasma Delipidation System-2 by Lipid Sciences, Inc. was used in clinical studies. Lipid Sciences, Inc. ceased business operations in 2012.

**Rationale**

This evidence review was originally created in July 1999 and updated regularly with searches of the MEDLINE database. The most recent update covers the period through July 2, 2015.

**LOW-DENSITY LIPOPROTEIN APHERESIS FOR FAMILIAL HYPERCHOLESTEROLEMIA**

In August 2008, the National Institute for Health and Clinical Excellence produced a systematic review of literature on familial hypercholesterolemia (FH), including low-density lipoprotein (LDL) apheresis in its management.{{NICE}, #49}

Although small RCTs were identified, they were not randomized to the treatment question of LDL apheresis versus other treatment but rather had apheresis in each arm. Therefore studies with lower level evidence informed reviewers’ conclusions. They did conclude that in homozygous individuals, apheresis is relatively safe and reduces LDL but were unable to draw definitive conclusions regarding newer statin agents in conjunction, or in lieu of, apheresis. They could not form recommendations on frequency of treatments. For heterozygous persons, the authors concluded that there was insufficient evidence to define entry criteria for apheresis treatment and recommended this intervention only in exceptional cases. The NICE review of the evidence is summarized below:

- There are no randomized controlled trials for treatment of FH homozygous individuals. However observational studies of FH homozygous individuals showed that treatment with LDL apheresis lowered LDL concentrations by 72% compared to use of multiple lipid-modifying maximal drug therapy.(3)
- Pre- and post studies showed that LDL apheresis treatment of individuals with FH who were primarily heterozygous and receiving lipid-lowering drugs demonstrated a total LDL-C percentage decrease ranging from 34% to 81%.
- In 2 small studies of individuals with heterozygous FH receiving LDL apheresis and lipid-modifying drug treatment, coronary artery disease regressed in 4 (16%) individuals and in 3 (13%) individuals in the 2 studies respectively.(4,5)
- The major limitation of these recommendations is that they were based on comparisons with older studies that used less well tolerated drugs or suboptimal statin doses. The current standard of care for homozygous and heterozygous FH has changed with the availability of PCSK9 inhibitors (evolocumab, alirocumab) and use of maximally tolerated statins doses.

Wang et al (2016) published a systematic review of lipid apheresis that included 15 studies in patients with homozygous and heterozygous FH treated with lipid
apheresis. None was a randomized controlled trial (RCT). Seven studies assessed patients with homozygous and heterozygous FH separately while the remaining made no such distinction. Studies reported a range for mean LDL-C reductions after apheresis of 57% to 75% for patients with homozygous FH and of 58% to 63% for patients with heterozygous FH. No hard end points such as cardiovascular (CV) outcomes and mortality were reported.

Assessment of the efficacy for a therapeutic intervention involves a determination whether an intervention improves health outcomes compared to available alternatives. The optimal study design for this purpose is an RCT that compares the therapeutic intervention with existing alternative treatments and includes clinically relevant measures of health outcomes. However, there are ethical limitations in the conduct of long-term RCTs that measure hard end points such as CV outcomes and mortality in patients with FH. An empirical review of multiple nonrandomized studies by Thompson (2013) showed that drastic lowering of LDL by lipoprotein apheresis increases longevity in homozygous FH and decreases CV morbidity in FH heterozygotes refractory to or intolerant of statins. However, most of the published guidelines and reviews have not incorporated the evidence gained from newer therapies such as antisense inhibitor of apoB synthesis (mipomersen), inhibitor of microsomal transfer protein (lomitapide), and PCSK9 inhibitors (alirocumab, evolocumab), which have been shown to reduce LDL-C levels in patients with homozygous and heterozygous FH. Any future RCTs to compare apheresis alone with no intervention or usual care or apheresis plus drug therapy with drug therapy alone will not be feasible and unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a last resort when maximally tolerated pharmacotherapy fails to achieve target LDL-C levels.

**Section Summary: Low-Density Lipoprotein Apheresis for Familial Hypercholesterolemia**

For patients with homozygous or heterozygous FH, no RCTs have evaluated lipid apheresis alone versus no intervention or usual care or apheresis plus drug therapy versus drug therapy alone. Multiple nonrandomized studies have shown that drastic lowering of LDL by lipoprotein apheresis increases longevity in homozygous FH and decreases CV morbidity in FH heterozygotes refractory to or intolerant of statins. Studies have reported reductions in LDL-C levels after apheresis in the mean range of 57% to 75% for patients with homozygous FH and 58% to 63% for patients with heterozygous FH. Currently direct evidence is insufficient to demonstrate that reductions in LDL-C levels seen with LDL apheresis will reduce adverse CV events. Any future RCTs to compare apheresis alone with no intervention or usual care or apheresis plus drug therapy with drug therapy alone will not be feasible and unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a last resort when maximally tolerated pharmacotherapy fails to achieve target LDL-C levels.

**LDL Apheresis for Non-FH-Associated Hyperlipidemia**

While the focus of most studies of LDL apheresis has been for FH-associated hypercholesterolemia, a smaller number of observational studies have evaluated
LDL apheresis in patients with lipoprotein(a) [Lp(a)]-hyperlipoproteinemia, hypercholesterolemia, or both, usually in conjunction with cardiovascular disease.

Leebmann et al (2013) reported on a prospective observational multicenter study of 170 patients treated with LDL apheresis for Lp(a)-hyperlipoproteinemia and progressive cardiovascular disease (CVD) despite receiving maximally tolerated lipid-lowering treatment.(8) During the 2-year treatment period with LDL apheresis, the authors reported a significant decrease in CV events compared with the 2-year period before treatment with LDL apheresis.

Heigl et al (2015) reported on a retrospective observational study of 118 consecutive patients treated at a single apheresis center with lipoprotein apheresis for either severe hypercholesterolemia or isolated Lp(a)-hyperlipoproteinemia with progressive CVD.(9) Most patients (n=111 [94%]) had hypercholesterolemia; 83 (70.3%) had Lp(a)-hyperlipoproteinemia, but isolated Lp(a)-hyperlipoproteinemia was the indication for lipid apheresis in only 35 (29.7%) patients. All patients were receiving maximally tolerated lipid-lowering medication and individually optimized cardiac medications before and during lipid apheresis treatment, although specifics about the lipid-lowering regimens used and reasons for treatment intolerance are not provided. Compared with the pre‒lipid apheresis period (average, 6.8 years), while patients were receiving chronic lipid apheresis treatment (average, 6.8 years), the average annual per-patient major adverse cardiac event rate decreased from 0.35 to 0.07 (79.7% reduction; p<0.001). The mean total LDL-C reduction was 32.1% from the pre-lipid apheresis period to steady state during lipid apheresis, while the mean total Lp(a) reduction was 56.4%. During 36,745 lipid apheresis treatments, there were unexpected adverse events in 1.1%, vascular problems in 2.1%, and technical problems in 0.08% of cases. Additional details about the study procedures and outcomes were described in an additional manuscript.(10)

Section Summary: LDL Apheresis in Patients With Non-FH Hypercholesterolemia and/or Lp(a)-Hyperlipoproteinemia
For patients with hypercholesterolemia and/or Lp(a)-hyperlipoproteinemia without known FH, noncomparative studies report improvements in lipid levels pre- and posttreatment. Randomized trials in patient populations that are well-characterized in terms of previous treatments, lipid levels, and comorbidities, are needed to demonstrate improvements in health outcomes.

LDL Apheresis for Nephrotic Syndrome
Altered lipid metabolism is a prominent abnormality in patients with nephrotic syndrome, which is defined as the presence of 3.5 g/d or higher proteinuria and hypoalbuminemia. Nephrotic syndrome may arise due to a variety of primary nephropathic and systemic diseases, with specific underlying disease prevalence varying based on patient age.

Two prospective single cohort studies have shown improvements in nephrotic syndrome with LDL apheresis. Muso et al (1999) developed an apheresis treatment protocol in 24 patients with focal segmental glomerulosclerosis (FSGS)
and nephrotic syndrome and 1 patient with minimal change nephrotic syndrome. Results showed rapid improvements of hyperlipidemia and a high incidence of remission at relatively short intervals. Hatori et al (2003) reported remission of nephrotic syndrome in 7 of 11 patients with steroid- and cyclosporine-resistant primary FSGS after initiating prednisone therapy with LDL apheresis. In 2014, Muso et al reported on the short-term results of a prospective observational study of LDL apheresis for drug-resistant nephrotic syndrome. Over 2 years, the study enrolled 58 patients with nephrotic syndrome resistant to primary medication (usually full-dose steroids or saturated cyclosporine A for at least 4 weeks) who were considered to be a candidate for LDL apheresis. The 58 patients underwent 64 episodes of LDL apheresis, of which 17 episodes were excluded from analysis due to missing urinary protein data or need to estimate urinary protein data (14 episodes), resolution of proteinuria before LDL apheresis (7 episodes), and treatment with LDL apheresis less than 4 weeks after the primary medication (2 episodes). Short-term clinical data for 47 episodes in 44 patients were analyzed. Resolution of nephrotic syndrome occurred in 25 episodes (53.1%). Longer term follow-up of this cohort is planned.

Section Summary: LDL Apheresis in Patients With Nephrotic Syndrome
Observational studies with short-term follow-up have reported that LDL apheresis may improve proteinuria and lipid abnormalities in patients with steroid-resistant nephrotic syndrome. Additional studies with concurrent controls and longer term follow-up are needed to determine that outcomes are improved for the use of LDL apheresis in nephrotic syndrome.

LDL Apheresis For Other Indications
There are several reports of LDL apheresis use for other indications, including sudden sensorineural hearing loss, nonarteritic acute anterior ischemic optic neuropathy, peripheral arterial disease, and preeclampsia, some of which are summarized here.

Bianchin et al reported on the use of HELP-apheresis in the treatment of sudden sensorineural hearing loss (SSNHL, which is an acute, mostly unilateral, inner ear disorder of unknown etiology), in a prospective, RCT. One hundred thirty-two patients with an acute, 1-sided SSNHL and a value of LDL-C greater than 120 mg/dL and/or fibrinogen greater than 320 mg/dL were randomly assigned to standard treatment, or standard treatment plus 1 session of HELP-apheresis. Standard treatment consisted of an infusion of 500 mL of glycerol, once a day for 10 days and intramuscular dexamethasone, 8 mg once a day for 10 days. Patient age range was 35 to 80 years (average, 60.4 years) for the first group and 31 to 83 years (average, 52.8 years) for the second group. In the HELP-apheresis plus standard therapy group, hearing recovery was observed in 75% of patients 24 hours after treatment and in 76.4%, 10 days after treatment. In the standard therapy group, the percentage of patients with hearing recovery was 41.7% after 24 hours and 45% after 10 days. The authors concluded that in patients with alterations in cholesterol and/or fibrinogen, HELP-apheresis treatment was an option in the treatment of SSNHL.
One study reported a case series of 11 patients with non-arteritic acute anterior ischemic optic neuropathy who were treated with 3 courses of LDL apheresis in conjunction with standard therapy of prednisone, salicylate, and pentoxyphylline. All patients reported improvements in visual function, but the contribution of the LDL apheresis cannot be evaluated in this small uncontrolled trial.

In 1 case series from Japan, 31 patients with peripheral artery disease (84% Fontaine symptom classification II) and an average LDL of 197 mg/dL underwent mean of 9.6 LDL-apheresis treatments. Improvement of at least 10% for symptomatic parameters (coldness, 89%; numbness, 64%; rest pain, 100%) was observed with no symptom worsening. Using the same 10% criterion, ankle brachial pressure index improved in 60% of limbs observed (worsened in 2%), and mean tolerated walking distance improved in 16 (70%) of 23 patients. No change was observed in any of the arterial occlusive lesions observed.

A series of 17 patients with severe diabetic foot ulcerations were treated with LDL apheresis on the hypothesis that drastically lowered fibrinogen, and possibly lowered plasma viscosity, would improve perfusion to the ischemic tissue and facilitate wound healing. Patients underwent between 1 and 7 treatments and were followed up for 2 to 73 months. LDL apheresis may have improved wound healing and reduced the risk of lower leg amputations; however, there was no control group or formal quantitative assessments of the lesions.

A European study reported on LDL-apheresis use in preeclampsia. Of the 13 patients with preeclampsia, 9 underwent between 1 and 7 heparin-mediated extracorporeal LDL precipitation (HELP) apheresis treatments and were reported to have experienced a mean 18 days’ (range, 3-49) longer gestation. Mortality was 1 in 9 in neonates of apheresis-treated mothers and 1 in 4 in neonates of mothers not treated with apheresis. The high risk of mortality in preeclampsia and the improved perinatal outcomes that accompany longer gestation are important reasons for further study of LDL apheresis.

The evidence on the use of LDL apheresis for conditions other than hypercholesterolemia and/or Lp(a)-hyperlipoproteinemia consists of small case series. Larger randomized trials with longer follow-up are needed to determine the impact of LDL apheresis on health outcomes for these conditions.

**THERAPEUTIC APERHERESIS WITH HIGH-DENSITY LIPOPROTEIN DELIPIDATION AND PLASMA REINFUSION**

Waksman et al reported a safety and feasibility RCT of 28 patients with acute coronary syndrome treated with therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion. Cardiac catheterization patients were randomized to receive 7 weekly therapeutic apheresis and plasma reinfusion with or without HDL delipidation. During catheterization and up to 2 weeks after the apheresis sessions were completed,
intravascular ultrasound (IVUS) was performed on a target vessel. Pre-beta-like HDL and alpha HDL levels in the plasma before and after delipidation changed from 5.6% to 79.1% and 92.8% to 20.9%, respectively. IVUS showed some evidence of regression in total atheroma volume in the delipidation patients, but this was not significant. No additional studies were identified.

The available evidence on therapeutic apheresis with selective HDL delipidation and plasma reinfusion is insufficient to draw conclusions. Further, larger well-designed RCTs with reports on health outcomes are needed.

SUMMARY OF EVIDENCE

Homozygous Familial Hypercholesterolemia
For individuals with homozygous FH who receive lipid apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies and 1 systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have shown that drastic lowering of LDL by lipoprotein apheresis increases longevity in homozygous FH. Studies have reported reductions in low-density lipoprotein cholesterol (LDL-C) levels after apheresis ranging from a mean of 57% to 75%. Currently the direct evidence is insufficient to demonstrate that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. Any future RCTs to comparing apheresis alone with no intervention or usual care or apheresis plus drug therapy with drug therapy alone will not be feasible and unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a last resort when maximally tolerated pharmacotherapy fails to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Heterozygous Familial Hypercholesterolemia
For individuals with heterozygous FH who receive lipid apheresis, the evidence includes multiple nonrandomized prospective and retrospective small cohort studies as well as a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have shown that drastic lowering of LDL using lipoprotein apheresis decreases cardiovascular morbidity in FH heterozygotes refractory to or intolerant of statins. Studies have reported reductions LDL-C levels after apheresis ranging from a mean of 58% to 63%. Currently the direct evidence is insufficient to demonstrate that reductions in LDL-C levels seen with LDL apheresis will reduce adverse cardiovascular events. Any future RCTs to comparing apheresis alone with no intervention or usual care or apheresis plus drug therapy with drug therapy alone will not be feasible and unlikely to resolve any clinical uncertainty because lipid apheresis is generally used as a last resort when maximally tolerated pharmacotherapy fails to achieve target LDL-C levels. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Nonfamilial Hypercholesterolemia
For individuals with non-FH who receive lipid apheresis, the evidence includes multiple nonrandomized (prospective and retrospective) cohort studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. These studies have reported improvements in lipid levels pre- and posttreatment. Randomized trials in patient populations, well-characterized in terms of previous treatments, lipid levels, and comorbidities, are needed to demonstrate improvements in health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Treatment-Resistant Nephrotic Syndrome
For individuals with treatment-resistant nephrotic syndrome who receive lipid apheresis, the evidence includes multiple nonrandomized prospective and retrospective cohort studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. These studies, which used variable schedules of LDL apheresis with short-term follow-up, have reported that LDL apheresis may improve proteinuria and lipid abnormalities in patients with steroid-resistant nephrotic syndrome. Additional studies with concurrent controls and longer term follow-up are needed to determine that outcomes are improved with use of LDL apheresis in nephrotic syndrome. The evidence is insufficient to determine the effects of the technology on health outcomes.

Sudden Sensorineural Hearing Loss
For individuals with sudden sensorineural hearing loss who receive lipid and fibrinogen apheresis, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. One RCT compared LDL apheresis with standard treatment of prednisolone, hydroxyethyl starch, and pentoxyphylline; it reported no statistically significant differences in hearing recovery between the 2 groups. The second RCT compared combination of a single lipid apheresis procedure plus standard treatment with standard treatment alone; it reported statistically significant differences in hearing recovery with the addition of apheresis to standard treatment. An a priori primary end point, power calculations, and statistical plan to control for type I error for multiple comparisons was not reported in the second trial. Further evaluation and replications of these findings are required given the conflicting reports. The evidence is insufficient to determine the effects of the technology on health outcomes.

Severe Diabetic Foot Ulcerations
For individuals with severe diabetic foot ulcerations who receive lipid apheresis, the evidence includes a single prospective case series. Relevant outcomes are symptoms, change in disease status, morbid events, and treatment-related morbidity. In the case series, patients underwent between 1 and 7 treatment procedures and were followed for 2 to 73 months. Authors reported improved wound healing and reductions in the risk of lower leg amputations, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.
Peripheral Artery Disease
For individuals with peripheral artery disease who receive lipid apheresis, the evidence includes a single prospective case series. Relevant outcomes are change in disease status and treatment-related morbidity. Improvements in symptomatic parameters such as coldness, numbness, and resting pain were reported, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Preeclampsia
For individuals with peripheral artery disease who receive lipid apheresis, the evidence includes a prospective case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Improvement in gestation was reported, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Non‒Arteritic Acute Anterior Ischemic Optic Neuropathy
For individuals with non‒arteritic acute anterior ischemic optic neuropathy who receive lipid apheresis, the evidence includes a prospective case series. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Improvement in visual outcomes was reported, but insufficient to ascertain the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Acute Coronary Syndrome
For individuals with acute coronary syndrome who receive selective high-density lipoprotein (HDL) delipidation and plasma reinfusion, the evidence includes an RCT. Relevant outcomes are overall mortality, disease-specific survival, change in disease status, morbid events, and treatment-related morbidity. Results have shown improvements in certain biochemical measures (eg, pre-beta-like HDL and alpha HDL levels). There was no significant change in atheroma volume. Larger randomized trials with longer follow-up and clinically relevant outcomes are needed to determine the impact of delipidated HDL plasma for acute coronary syndrome. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Institute for Health and Care Excellence
National Institute for Health and Care Excellence’s 2008 guidance on familial hypercholesterolemia (FH) states the following:

“Healthcare professionals should consider offering LDL [low-density lipoprotein] apheresis for the treatment of adults and children/young people with homozygous FH. The timing of initiation of LDL apheresis should depend
on factors such as the person's response to lipid-modifying drug therapy and presence of coronary heart disease.”

“In exceptional instances (such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy), healthcare professionals should consider offering LDL apheresis for the treatment of people with heterozygous FH. This should take place in a specialist center on a case-by-case basis and data recorded in an appropriate registry.”{(NICE), #49}

**European Atherosclerosis Society**

In 2014, the European Atherosclerosis Society issued guidelines on the management of homozygous FH, which made the following recommendations about the use of lipid apheresis:

“This Consensus Panel recommends that lipoprotein apheresis be considered in patients with HoFH [homozygous familial hypercholesterolemia]. Treatment should be started as soon as possible, ideally by age 5 and not later than 8 years.”(22)In 2013, the European Atherosclerosis Society issued a consensus statement on the management of FH, which made the following recommendations about the use of lipid apheresis: “This Consensus Panel recommends that lipoprotein apheresis be considered in patients with treatment resistant HeFH [heterozygous familial hypercholesterolemia].”(23)

**International FH Foundation**

In 2015, the International FH Foundation published integrated guidelines on the care of FH, which make the following recommendations about the use of lipid apheresis (see Table 1).(24)

<table>
<thead>
<tr>
<th>Table 1: International FH Foundation Guidelines on Use of Lipid Apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline</td>
</tr>
<tr>
<td>LA should be considered in all patients with homozygous or compound heterozygous FH (i.e. homozygous FH phenotype) and carried out in a dedicated centre with the relevant expertise.</td>
</tr>
<tr>
<td>LA should be considered in patients with heterozygous FH with CHD who cannot achieve LDL-cholesterol targets despite maximal drug therapy or because they cannot tolerate statins.</td>
</tr>
<tr>
<td>LA should be considered in children with homozygous FH by the age of five and no later than eight years.</td>
</tr>
<tr>
<td>Diet and drug therapy to lower LDL cholesterol should be continued during treatment with LA.</td>
</tr>
</tbody>
</table>

CHD: FH: familial hypercholesterolemia; LA: lipoprotein apheresis; LDL: low-density lipoprotein.

**American Society for Apheresis**

In 2013, the American Society for Apheresis issued guidelines on use of apheresis in 78 conditions (see Table 2).(25)

<table>
<thead>
<tr>
<th>Table 2: American Society for Apheresis Guidelines on Use of Apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline</td>
</tr>
<tr>
<td>Low-density lipoprotein apheresis for homozygous FH is</td>
</tr>
</tbody>
</table>
Heterozygous FH is considered appropriate as a second-line treatment. Lipoprotein (a) hyperlipoproteinemia is considered first-line treatment. Peripheral vascular diseases and Phytanic acid storage disease (Refsum disease) are considered grade 1B recommendations. Sudden sensorineural hearing loss is considered grade 2A.

FH: familial hypercholesterolemia.

a Grade 1A: strong recommendation, high-quality evidence; grade 1B: strong recommendation, moderate quality evidence; grade 2A: weak recommendation, high-quality evidence; grade 2C: weak recommendation, low quality evidence. b Optimum role not established.

National Lipid Association

In 2011, the National Lipid Association issued guidelines on the treatment of FH. They recommended LDL apheresis for FH in patients who do not adequately respond to maximum tolerated drug therapy after 6 months of treatment as follows with:

- Functional homozygous with LDL cholesterol ≥300 mg/dL (or non-HDL cholesterol ≥330 mg/dL);
- Functional heterozygous with LDL cholesterol ≥300 mg/dL (or non-HDL cholesterol ≥330 mg/dL) and 0-1 coronary heart disease risk factors;
- Functional heterozygous with LDL cholesterol ≥200 mg/dL (or non-HDL cholesterol ≥230 mg/dL) and high risk characteristics such as ≥2 risk factors or high lipoprotein (a) ≥50 mg/dL; or
- Functional heterozygotes with LDL cholesterol ≥160 mg/dL (or non-HDL cholesterol ≥190 mg/dL) and very high risk characteristics (established coronary heart disease, other cardiovascular disease, or diabetes).

A 2006 scientific statement from American Heart Association (AHA) for the treatment of heterozygous FH has indicated that adults should be treated with available pharmacotherapy with an initial goal of reducing LDL-C by at least 50%, usually with a statin and treatment should be intensified based on response. It also stated that there are no data to inform pediatric treatment goals, whether to target an LDL-C level of less than 100 or 130 mg/dL or to aim to achieve a 50% reduction in LDL-C from baseline.

For homozygous patients, lipid-lowering therapy, usually statins, should be instituted at diagnosis and as early as possible. Among the 2 currently available PCSK9 inhibitor in the United States, only alirocumab has been approved for the homozygous FH patients in whom it was shown that addition of alirocumab to standard treatment (statins and ezetimibe but not lipid apheresis) reduces low-density lipoprotein cholesterol (LDL-C) by an additional 31%. AHA recommended that lipid apheresis should be considered by 5 years of age or earlier in exceptional circumstances and should be used after maximally tolerated pharmacotherapy fails to achieve target LDL-C levels. LDL-C selection criteria for lipid apheresis include a reduction in LDL-C of less than 50% by other treatments and residual severe LDL-C elevation of more than 300 mg/dL or more than 200 mg/dL with prevalent cardiovascular disease.
Ministry of Health of Ontario
The Medical Advisory Secretariat of the Ministry of Health of Ontario published an evidence-based analysis of the available literature for the period of January 1998 to May 2007.(29) The authors concluded that, for homozygous FH patients, there is a strong recommendation based on low- to very low-quality evidence that the benefits of LDL apheresis outweigh risks and burdens. In contrast, the authors offer a weak recommendation based on low- to very low quality evidence favoring apheresis for heterozygous people. For the small number of heterozygous people who are intolerant to lipid-lowering medications, or who cannot reach lipid level targets on maximal diet and medication, the authors remark that LDL apheresis is likely as beneficial and less likely to have fewer adverse effects, as plasmapheresis.

No guidelines on therapeutic apheresis with selective HDL delipidation and plasma reinfusion were identified.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

MEDICARE NATIONAL COVERAGE
National Coverage Decision 110.14 APHERESIS (therapeutic pheresis) lists the indications for which apheresis is a covered benefit in cellular and immune-complex mediated disorders. There is no determination for hypercholesterolemia or LDL apheresis.(30)

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01967355</td>
<td>Prolongation of Pregnancy in Preeclampsia by Therapeutic Lipid Apheresis</td>
<td>15</td>
<td>Jun 2017</td>
</tr>
<tr>
<td>NCT01518205</td>
<td>HELP-Apheresis in Diabetic Ischemic Foot Treatment (H.A.D.I.F): an RC Trial to Evaluate the Effect of LDL-apheresis on the Recovery of Diabetic Ulcers in Patients With Peripheral Vasculopathy Not Susceptible to Revascularization</td>
<td>132</td>
<td>Dec 2017</td>
</tr>
</tbody>
</table>
Unpublished

NCT: national clinical trial.

References:
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Lipid apheresis in the treatment of severe, refractory hypercholesterolemia. TEC Assessments 1999; Volume 14, Tab 3. PMID


**Billing Coding/Physician Documentation Information**

**S2120** Low density lipoprotein (LDL) apheresis using heparin-induced extracorporeal LDL precipitation

**36516** Therapeutic apheresis; with extracorporeal selective adsorption or selective filtration and plasma reinfusion

**0342T** Therapeutic apheresis with selective HDL delipidation and plasma
reinfusion

**ICD-10 Codes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E78.00</td>
<td>Pure hypercholesterolemia, unspecified</td>
</tr>
<tr>
<td>E78.01</td>
<td>Familial hypercholesterolemia</td>
</tr>
</tbody>
</table>

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

- **4/1/05**: New policy.
- **4/1/06**: No policy statement changes.
- **4/1/07**: No policy statement changes.
- **4/1/08**: No policy statement changes.
- **4/1/09**: Policy statement clarified that other uses, e.g., use in preeclampsia, are considered investigational (previously considered not medically necessary).
- **4/1/10**: No policy statement changes.
- **4/1/11**: No policy statement changes.
- **4/1/12**: No policy statement changes.
- **4/1/13**: No policy statement changes.
- **4/1/14**: No policy statement changes.
- **11/1/14**: Added policy statement indicating therapeutic apheresis with selective high-density lipoprotein (HDL) delipidation and plasma reinfusion is investigational; title changed to Lipid Apheresis. Added CPT 0342T.
- **4/1/15**: No policy statement changes.
- **4/1/16**: No policy statement changes.
- **4/1/17**: No policy statement changes.
- **7/1/17**: “6-month trial” removed from the second medically necessary policy statement. Additional specific examples added to the LDL apheresis investigational for other uses statement. The Policy Guidelines section was revised by deleting the statement “Maximum tolerated drug therapy is defined as a trial of drugs from at least 2 separate classes of hypolipidemic agents such as bile acid sequestrants, HMG-CoA reductase inhibitors, fibric acid derivatives, or niacin/nicotinic acids.”

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